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Applicant(s): SANKYO COMPANY, LIMITED.
Inventor(s): Tokio KURASAWA et al.
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Title of Invention: Method of producing ketothiphenefumate-containing eye water

Number of Claim(s): 1

SPECIFICATION

1. Title of the Invention

METHOD OF PRODUCING KETOTHIPHENE FUMARATE-CONTAINING
EYE WATER

2. What is claimed is:

A method of producing a ketothiphenic fumarate-
containing eye water, characterized in that polyvalent
alcohols and similars are used as an isotonizing agent.

3. DETAILED DESCRIPTION OF THE INVENTION

{Objects of the Invention}

The present invention relates to a method of producing
an eye water.

In general, it is the most important point for an eye
water that said eye water is isotonic to an extent nearly
same as a tear. And, in order to isotonize the eye water,
an electrolyte, such as sodium chloride, has been usually
used.

Although ketothiphenic fumarate is an oral asthmatic
medicine, it has been reported that it is useful also as an
eye water (Mikuni et al.: Byoin Yakugaku., 10, 3 (1984), pp
171 - 176).

However, ketothiphenic fumarate alone is unsuitable as
the eye water and an isotonizing agent is required. But,
it has been found that if an electrolyte, which has been

usually used as an isotonizing agent, is used, a long-term stability is remarkably spoiled.

So, the present inventors have discovered a method of producing a ketothiphenic fumarate-containing stable eye water as a result of their earnest study aiming at an improvement of such the disadvantage to achieve the present invention.

[Construction of the Invention]

The present invention relates to a method of producing a ketothiphenic fumarate-containing eye water using polyvalent alcohols and similars as an isotonizing agent.

X Said polyvalent alcohols and similars used in the present invention include saccharides consisting of oligosaccharides, such as monosaccharides, for example D-erythrose, D-ribose, D-xylose, D-glucose, D-mannose, D-fructose and L-rhamnose, disaccharides, for example sucrose, maltose and lactose, trisaccharides, for example raffinose, and tetrasaccharides, for example stachyose, and saccharoalcohols and similars, such as erythritol, xylitol and D-mannitol, in addition to alcohols and similars, such as glycerin, propylene glycol, trimethylene glycol, pentaerythritol and polyethylene glycol, having two or more hydroxyl groups.

Said polyvalent alcohols and similars are added in a quantity necessary for the isotonization and it is different

depending upon a kind of polyvalent alcohol used.

In the present invention, an antiseptic, such as benzalconium chloride, can be suitably used according to the usual way.

The eye water according to the present invention is produced by the usual way. For example, ketothiphene fumarate, polyvalent alcohols and similars and an antiseptic in case of need are dissolved in water. A base, such as sodium hydroxide, is added to the obtained solution to adjust the pH at a suitable value and then the solution is subjected to a sterilized filtration followed by subdividing into sterilized containers to obtain the eye water.

[Effects of the Invention]

The present invention will be below described in more detail with reference to preferred embodiments.

EXAMPLE 1

Ketothiphene fumarate of 1.0 g, benzalconium chloride of 0.1 g and mannitol of 50 g were dissolved in distilled water of about 800 ml. Then, a suitable quantity of sodium hydroxide was added to the resulting solution to adjust the pH at 5.0 followed by adding distilled water so that the whole quantity may amount to 1,000 ml.

EXAMPLE 2

The treatment was carried out in the same manner as in EXAMPLE 1 excepting that glucose of 60 g was used in place

EXAMPLE 4

The treatment was carried out in the same manner as in EXAMPLE 1 excepting that propylene glycol of 21 g was used in place of D-mannitol of 50 g.

EXAMPLE 5

The treatment was carried out in the same manner as in EXAMPLE 1 excepting that polyethylene glycol 200 of 50 g was used in place of D-mannitol of 50 g.

EXAMPLE 6

The treatment was carried out in the same manner as in EXAMPLE 1 excepting that polyethylene glycol 400 of 100 g was used in place of D-mannitol of 50 g.

COMPARATIVE EXAMPLE 1

The treatment was carried out in the same manner as in EXAMPLE 1 excepting that sodium chloride of 10 g was used in place of mannitol of 50 g.

COMPARATIVE EXAMPLES 2 to 6

The treatment was carried out in the same manner as in COMPARATIVE EXAMPLE 1 by the use of various electrolytes.

<u>No. of COMPARATIVE EXAMPLES</u>	<u>Electrolyte</u>	<u>Quantity added</u>
2	KCl	10 g/1.000 ml
3	Na ₂ SO ₄	20
4	(NH ₄) ₂ SO ₄	20
5	CH ₃ COONa	20
6	NH ₄ Cl	20

TEST EXAMPLES

An ampule of 2 ml was filled with the eye water obtained in EXAMPLES 1 to 6 and COMPARATIVE EXAMPLES 1 to 6 to measure a change after the lapse of 8 hours and 16 hours at 100°C.

The results are shown in Table 1.

As clear from Table 1. in the case where polyvalent alcohols and similars were added, ketothiphen fumarate was stable in comparison with the case where the electrolytes were added.

Table 1

	Content of ketothiophene fumarate (%)		
	100°C		
	0	8	16
	hour	hours	hours
EXAMPLE 1	100	88	86
2	100	93	89
3	100	90	87
4	100	85	80
5	100	86	78
6	100	84	80
COMPARATIVE EXAMPLE 1	100	50	39
2	100	59	46
3	100	83	76
4	100	77	72
5	100	64	57
6	100	43	29